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10/829,015	04/20/2004	Mark Chee	3047.2	5980

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,015	CHEE, MARK	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-29* is/are pending in the application.

4a) Of the above claim(s) *26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 16-25, in the reply filed on 10/04/2006 is acknowledged.

2. Claims 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/04/2006.

A first action on the merits of claims 16-25 follows.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Provisional Application 60/041, 435 filed 20 March 1997 does not provide adequate support for claims 21, 22, and 23. While '435 describes a tiling array the specification does not teach tiling arrays of both strands, duplicate arrays or hybridization of a second array with lower stringency than other duplicate array. Therefore the effective filing date for claims 21-23 is 3/19/1998.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims are drawn to a method of analyzing a target nucleic acid comprising: designing a first probe array comprising a plurality of probes plurality of probes complementary to a region of a reference genome of a first species; hybridizing the target nucleic acid to the first probe array, wherein the target nucleic acid is derived from a target genome of a second species; estimating the sequence of said target nucleic acid; designing a second probe array comprising a plurality of probes complementary to the estimated sequence of the target nucleic acid; and reestimating the sequence of said target nucleic acid. In view of the open claim language "comprising", the probes of the second probe array encompass all probes in the first probe array. As such, hybridization to the same array is encompassed by the claim language. Furthermore, the claims are drawn to probe arrays, but do not require a solid support.

The rejections are based on the broad interpretation of species as defined by onelook.com:

> Species • ***noun***: a specific kind of something (Example: *"A species of molecule"*) (www.onelook.com/?loc=lemma2&w=species).

5. Claims 16, 19, 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Kozal et al (Nature Medicine, 1996, volume 2, pages 753-759).

Regarding Claim 16, Kozal et al disclose a method of analyzing a target comprising designing an array of probes, not comprising every possible probe of a given length, but comprising a probe set complementary to a known reference sequence (e.g. PR gene), hybridizing the target to the array wherein the target is a variant of the

reference (i.e. "extremely variable" USA HIV-1 clade B proteases, Abstract) determining relative hybridization of the probes to the target and estimating the sequence of the target (page 757, lines 1-8 and Fig 5b, left most quadrant containing 11, 14, 17 and 20 base probes) and providing a further array of probes comprising a probe set comprising probes complementary to the estimated sequence (Fig 5b, second quadrant from the left containing 11, 14, 17 and 20 base probes overlapping with the probes is the left quadrant).

Figure 5 illustrates the PR chip and figure 5(b) specifically illustrates 5 different hybridization reactions wherein at each hybridization loci, the sequence of the target is estimated and at each subsequent hybridization loci, the sequence is re-estimated. The hybridization and sequence re-estimation is repeated until each base is determined thereby analyzing the target (page 756-757). It is noted that the claims do not require separate, distinct and/or sequential probe preparation or hybridization steps. The second designing step merely requires that the array comprises probes complementary to the estimated sequence. This recitation encompasses the same array with the same probes as the first designing step because the array of the first designing step comprises probes complementary to the estimated sequence.

Kozal et al discloses the method wherein the target is a species variant of the reference (i.e. variant of the USA HIV-1 clade B proteases, Abstract)

Regarding Claims 19, Kozal et al disclose the method wherein the target shows 80- 95% identity with the reference (i.e. the analyzed targets differ from the reference

382 base region by 9, 6, 3 and 4 bases, page 754, Table 1 spanning page 755, first paragraph).

6. Claims 16 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Skiena (U.S. Patent No. 5,683,881, issued 4 November 1997).

Regarding claim 16, Skiena teaches interactive sequencing by hybridization method with a plurality of nucleic acid probes (see column 4, lines 57-60). Skiena teaches hybridization of a target to a first probe array, taking the results from this experiment and use the results to design a customized sequencing chip to resolve any ambiguities, thus determining the complete sequence of the target (see column 4 lines 16-22). Skiena does not teach the using probes complementary to the reference genome of a first species for the first probe array and the use of a target nucleic acid from the genome of a second species.

With regards to claim 25, Skiena teaches his method results in megabase de novo sequencing (see column 4, lines 50-51).

7. Claims 16-19, and 21-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Chee et al (WO 95/11995, published 4 May 1995).

Regarding Claim 16, Chee et al disclose a method of analyzing a target comprising designing an array of probes, not comprising every possible probe of a given length, but comprising a probe set complementary to a known reference sequence (page 18, lines 2-12 and 25-28), hybridizing the target to the array wherein the target is a variant of the reference determining relative hybridization of the probes to the target (e.g. page 12, lines 24-page 13, line 8; Fig 12; and page 30, lines 3-20) and estimating

the sequence of the target (i.e. sampling each nucleotide of interest several times to call a nucleotide at position, page 18, lines 19-23) and providing a further array of probes comprising a second probe set comprising probes complementary to the estimated sequence (e.g. to sample adjacent nucleotides of the reference sequence, page 18, lines 21-23 i.e. tiled probe sets (page 21-33) and re-estimating the sequence from the relative hybridization i.e. the sequence is estimated at each position whereby all estimation at all positions subsequent to the first estimation are "re-estimations" of the sequence, e.g. page 8, line 16-page 9, line 11 and page 71, line 30-page 72, line 24).

Chee et al disclose the method wherein the target is a species variant of the reference (page 18, lines 2-4)

Regarding Claims 19, Chee et al disclose the method wherein the target shows 80-95% identity with the reference (page 19, lines 11-14).

Regarding Claims 17, 18, 19, 24, 25, Chee et al disclose the method wherein the reference sequence is at least 10kb, 1000kb or full-length genome (whole) (page 20, line 36-page 21, line 8).

With regards to claim 21, Chee et al teaches probes that are complementary to coding and non-coding strands (see page 29, lines 10-12).

With regards to claim 22, Chee et al teaches hybridization of 5 clones to separate chips for sequence comparison (see page 112, lines 34-35). Each chip is a duplicate probe array.

With regards to claim 23, Chee teaches the use of different stringency conditions (see page 102, lines 27-28).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (WO/1995/11995) in view of Villenger et al (Journal of immunology, (1995) volume 155, pages 3946-3954).

Chee et al disclose a method of analyzing a target comprising designing an array of probes, not comprising every possible probe of a given length, but comprising a probe set complementary to a known reference sequence (page 18, lines 2-12 and 25-28), hybridizing the target to the array wherein the target is a variant of the reference determining relative hybridization of the probes to the target (e.g. page 12, lines 24-page 13, line 8; Fig 12; and page 30, lines 3-20) and estimating the sequence of the target (i.e. sampling each nucleotide of interest several times to call a nucleotide at position, page 18, lines 19-23) and providing a further array of probes comprising a second probe set comprising probes complementary to the estimated sequence (e.g. to sample adjacent nucleotides of the reference sequence, page 18, lines 21-23 i.e. tiled probe sets (page 21-33) and re-estimating the sequence from the relative hybridization i.e. the sequence is estimated at each position whereby all estimation at all positions

subsequent to the first estimation are "re-estimations" of the sequence, e.g. page 8, line 16-page 9, line 11 and page 71, line 30-page 72, line 24). Chee et al disclose the method wherein the target is a species variant of the reference (page 18, lines 2-4). Chee et al disclose the method wherein the target shows 80-95% identity with the reference (page 19, lines 11-14).

Chee et al does not the use of a reference genome from a human and a target genome from a primate.

However, Villenger teaches the use of human probes (first species) (see table 1, page 3947) to clone and sequence nonhuman primate (second species) equivalents of human genes (see 3946, 2nd column last 3 lines)(claims 16, 19, 20). Villenger teaches that primates are valuable models for the study of a broad range of disciplines.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Chee's method of analyzing nucleic acids by using human probes to detect and sequence primate nucleic acids as taught by Villenger. The ordinary artisan would be motivated to improve Chee's method of analyzing nucleic acids with the use of human probes to detect and sequence primate nucleic acids because Villenger teaches it allows the detection and isolation of human genes in an important model system for a broad range of disciplines.

10. Claims 16-20, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skiena (U.S. Patent No. 5,683,881, issued 4 November 1997) in view of Villenger et al (Journal of immunology, (1995) volume 155, pages 3946-3954).

Skiena teaches interactive sequencing by hybridization method with a plurality of nucleic acid probes and includes the step of selecting a subsequent set of probes using an adaptive, interactive algorithm. (See column 4, lines 50-65). Skiena teaches hybridization of a target to a first probe array, taking the results from this experiment and use the results to design a customized sequencing chip to resolve any ambiguities, thus determining the complete sequence of the target (see column 4 lines 16-22). Skiena does not teach the using probes complementary to the reference genome of a first species for the first probe array and the use of a target nucleic acid from the genome of a second species.

Skiena teaches the target molecule is a genome (see column 7, lines 35-40), but is silent on the length being at least 10% of the genome (claim 17), whole genome (claim 18 and 24) or 1Mb (claim 25) of genome. However it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Skiena's method of sequence estimation to estimate any length of the genome.

However, Villenger teaches the use of human probes (first species) (see table 1, page 3947) to clone and sequence nonhuman primate (second species) equivalents of human genes (see 3946, 2nd column last 3 lines)(claims 16, 19, 20). Villenger's use of primates as a target molecule encompasses claims 19 and 20. Villenger teaches that primates are valuable models for the study of a broad range of disciplines.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Skiena's method of interactive sequencing by using human probes to detect and sequence primate nucleic acids as

taught by Villenger. The ordinary artisan would be motivated to improve Skiena's method of interactive sequencing with the use of human probes to detect and sequence primate nucleic acids because Villenger teaches it allows the detection and isolation of human genes in an important model system for a broad range of disciplines.

11. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Skiena (U.S. Patent No. 5,683,881, issued 4 November 1997and Villenger et al (Journal of immunology, (1995) volume 155, pages 3946-3954) as applied to claims 16-20, 24 and 25 above, and further in view of Erlich (US Patent 5310893, issue May 10, 1994).

The teachings of Skiena and Villenger are set forth above. Skiena and Villenger do not teach the use of probe arrays tiling both strands of the reference genome.

However, Erlich teaches the method wherein the probes comprise at least 4 probe sets wherein each probe in a set includes at least 6 nucleotides complementary to a subsequence of the reference wherein relative binding for the probes is determined to estimate the sequence of the target (Column 25, lines 1-57). Erlich further teaches the use of probes to coding and non-coding strands (column 25, lines 60-63). Erlich teaches his method allows for rapid, convenient, practical, and reproducible method of genotyping.

12. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skiena (U.S. Patent No. 5,683,881, issued 4 November 1997) and Villenger et al (Journal of immunology, (1995) volume 155, pages 3946-3954) as applied to claims 16-20, 24 above, and further in view of Maskos et al (Nucleic acids Research (1993) volume 21, pages 2267-2268).

The teachings of Skiena and Villenger are set forth above. Skiena and Villenger do not teach the use of duplicate probe arrays with lower stringencies.

However, Maskos et al teaches the use of multiple probe arrays with high stringency hybridization (52°) and lower stringencies 32°(see figure 2) to optimize hybridization conditions (see page 2267, 2nd column, line 6).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Skiena and Villenger's method of nucleic acid estimating by using the duplicate probe arrays and hybridization stringencies of Maskos. The ordinary artisan would be motivated to improve Skiena and Villenger nucleic acid estimating method with Maskos use of duplicate arrays and lower hybridization stringencies because Maskos teaches they allow for optimization of hybridization.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-20, 24 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4 and 10 of currently allowed US Patent 7144699. Although the conflicting claims are not identical, they are not patentably distinct from each other because co-extensive in scope.

Claim 16 of instant application is drawn to a method of analyzing a target nucleic acid designing a first probe array comprising a plurality of probes complementary to a region of a reference genome of a first species; hybridizing the target nucleic acid to the first probe array, wherein the target nucleic acid is derived from a target genome of a second species; estimating the sequence of said target nucleic acid; designing a second probe array comprising a plurality of probes complementary to the estimated sequence of the target nucleic acid; and re-estimating the sequence of said target nucleic acid. Claim 1 of '699 teaches (a) designing an array of probes based on a known reference sequence, the array comprising a probe set comprising probes complementary to and spanning the known reference sequence, the probes immobilized on at least one support; (b) hybridizing the target nucleic acid to the array of probes, wherein the target nucleic acid has a sequence which is a variant of the reference sequence and provided the array of probes does not contain every possible probe sequence of a given length; (c) determining the relative hybridization of the probes to the target nucleic acid, (d) estimating the sequence of the target nucleic acid from the relative hybridization of the probes; (e) designing a further array of probes

based on the estimated sequence obtained in step (d), the further array comprising a probe set comprising probes complementary to and spanning the estimated sequence of the target nucleic acid, the probes immobilized on at least one support and provided the further probe array does not contain every possible probe sequence of a given length; (f) hybridizing the target nucleic acid to the further array of probes; (g) determining the relative hybridization of the probes of the further array to the target nucleic acid; (h) reestimating the sequence of the target nucleic acid from the relative hybridization of the probes of the further array.

Claim 17 of instant application further draws claim 16 to a region of the reference genome comprising at least 10% of the genome and the whole genome, respectively. Claim 11 of '699 teaches reference sequence of at least 90% of human genome.

14. Claims 18-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1, 5, 10, 11 of U.S. Patent No. 7144699 in view of Chee et al (WO/1995/11995).

Claim 1 of '699 teaches (a) designing an array of probes based on a known reference sequence, the array comprising a probe set comprising probes complementary to and spanning the known reference sequence, the probes immobilized on at least one support; (b) hybridizing the target nucleic acid to the array of probes, wherein the target nucleic acid has a sequence which is a variant of the reference sequence and provided the array of probes does not contain every possible probe sequence of a given length; (c) determining the relative hybridization of the probes to the target nucleic acid, (d) estimating the sequence of the target nucleic acid

from the relative hybridization of the probes; (e) designing a further array of probes based on the estimated sequence obtained in step (d), the further array comprising a probe set comprising probes complementary to and spanning the estimated sequence of the target nucleic acid, the probes immobilized on at least one support and provided the further probe array does not contain every possible probe sequence of a given length; (f) hybridizing the target nucleic acid to the further array of probes; (g) determining the relative hybridization of the probes of the further array to the target nucleic acid; (h) reestimating the sequence of the target nucleic acid from the relative hybridization of the probes of the further array. Claim 11 of '699 teaches reference sequence of at least 90% of human genome.

Claim 19 of instant application is taught by claim 5 of '699.

Claim 20 on instant application is drawn to the use of a human reference sequence and primate target sequence. Claim 5 of '699 teaches the use of a human reference sequence and primate target sequence.

Claim 24 of instant application is drawn to hybridizing nucleic acids representing the whole genome. Claim 11 of '699 teaches the use of at least 90% of genome, which is representative of the whole genome.

Claim 25 of instant invention is drawn to hybridizing pools of 1 Mb sequences of the genome. Claim 10 of '699 teaches the use of sequences of at least 1000kb, or 1Mb.

The claims of the instant application do not teach the reference genome is the whole genome (claim 18).

However, Chee et al teaches the use of an entire genome allows broader comparisons (see page 18, lines 5-7).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of the entire genome as taught by Chee. The ordinary artisan would be motivated to perform a broader detection.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JEANINE A. GOLDBERG
PRIMARY EXAMINER
12/7/06

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert